Claims

1. A pharmaceutical composition comprising an apolipoprotein construct having the general formula

- apo-A-X,

- where apo-A is an apolipoprotein component selected from the group consisting of apolipoprotein AI, apolipoprotein AII, apolipoprotein AIV, a functional analogue or variant thereof,

- and X is a heterologous moiety comprising at least one compound selected from the group consisting of an amino acid, a peptide, a protein, a carbohydrate, and a nucleic acid sequence,

- with the proviso that when the construct consists of exactly two identical, native apolipoproteins these are linked serially.

2. The composition of claim 1, further comprising a spacer between the apo-A component and X, wherein the spacer comprises a spacer peptide comprising at least two amino acids, such as at least three amino acids, for example at least five amino acids, such as at least ten amino acids, for example at least 15 amino acids, such as at least 20 amino acids, for example at least 30 amino acids, such as at least 40 amino acids, for example at least 50 amino acids, such as at least 60 amino acids, for example at least 70 amino acids, such as at least 80 amino acids, such as at least 90 amino acids such as approximately 100 amino acids.

3. The composition according to claim 2, wherein the spacer is essentially non-immunogenic, and/or is not prone to proteolytic cleavage and/or does not comprise any cystein residues.

4. The composition according to claim 2, wherein the three-dimensional structure of the spacer is linear or substantially linear.

5. The composition according to claim 2, wherein the spacer peptide comprises the amino acid sequence GTKVHMK from tetranectin, amino acid sequence PGTSGQQPSVGQQ and GTSGQ from the connecting strand 3 from human fibronectin, PKPSTPPGSS from the upper hinge region of murine IgG_3, SGGTSGSTSGTGST, AGSSTGSSTGPGSTT or GGSGGAP.

6. The composition of claim 1, wherein the component X is linked by a covalent link to the N-terminal or the C-terminal amino acid of apo-A.

7. The composition of claim 1, wherein the protein or peptide comprises at least one mammalian protein.

8. The composition according to claim 7, wherein the mammalian protein is a human protein.

9. The composition according to claim 7, wherein the protein is non-immunogenic.

10. The composition of claim 7, wherein the protein comprises at least one protein selected from the group comprising albumin, more preferably serum albumin, the serine protease fragment of plasminogen or another serine protease engineered to be inactive by disruption of the catalytic triad, and the constant region of the heavy chain of immunoglobulins.

11. The composition according to claim 7, wherein the protein comprises at least one amphipatic helix containing apolipoprotein.

12. The composition according to claim 1, wherein the component X comprises at least one apolipoprotein A-I, apolipoprotein A-II, apolipoprotein A-IV, Apolipoprotein E, an analogue or variant thereof.

13. The composition of claim 12, wherein the analogue or variant is capable of eliciting substantially the same physiological response as the apolipoprotein-A-I, A-II or A-IV.

14. The composition of claim 7, wherein the peptide constituting the component X comprises more than 1 amino acids such as more than 2 amino acids, for example more than 5 amino acids, such as more than 10 amino acids, for example more than 15 amino acids, such as more than 20 amino acids, such as more than 30 amino acids, for example more than 40 amino acids, such as more than 50 amino acids, for example more than 75 amino acids, such as more than 100 amino acids, for example more than 200 amino acids, such as more than 300 amino acids, for example more than 400 amino acids, such as more than 500 amino acids, for example more than 600 amino acids, such as more than 700 amino acids, for example more than 800 amino acids, such as more than 900 amino acids, for example more than 1000, 1250, 1500, 2000, or 2500 amino acids..

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15. The composition of claim 1, wherein the oligomerising module is a dimerising module.

16. The composition of claim 1, wherein the oligomerising module is a trimerising module.

17. The composition of claim 1, wherein the oligomerising module is a tetramerising modul.

18. The composition of claim 1, wherein the oligomerising module is a multimerising module.

19. The composition of claim 1, wherein the oligomerising module is of non-peptide nature.

20. The composition of claim 16, wherein the trimerising module comprises an amino acid sequence, capable of mediating interchain recognition, trimerisation and alignment of three polypeptide chains.

21. The composition of claim 16, wherein the trimerising module is from tetranectin.

22. The composition of claim 21, wherein the tetranectin trimerising module is capable of forming a stable complex with other tetranectin trimerising modules.

23. The composition of the claims 22, wherein the stable complex includes a coiled coil structure.

24. The composition of claim 23, wherein the coiled coil structure is a triple alpha helical coiled coil.

25. The composition of the claim 21, wherein the trimerising module comprises two tetranectin trimerising modules linked by a spacer moiety, which allows both of the two tetranectin trimerising modules to take part in a complex formation with a third tetranectin trimerising module not being part of the apolipoprotein construct.

26. The composition of the claims 21, wherein at least one tetranectin trimerising module is selected from the group consisting of human tetranectin, murine tetranectin or C-type lectin of human, bovine or shark cartilage.

27. The composition of the claims 21, wherein the tetranectin trimerising module comprises a sequence having at least 68 % identity with the sequence of SEQ ID NO 12.

28. The composition of claim 27, wherein the cystein residue no. 50 is substituted by a serine residue, a threonine residue, or a methionine residue.

29. The composition of claim 16, wherein the trimerisation module has at least 68 % sequence identity with the Trip A module (SEQ ID NO 13).

30. The composition of claim 16, comprising the trimerisation module from the collectin neck region.

31. The composition of claim 1, further comprising at least one carbohydrate moiety.

32. The composition of claim 1, having a half-life of at least the half-life of native Apo A-I, A-II or A-IV, preferably at least 2 times higher, more preferably at least 3

times higher such as 4 times, more preferably at least 5 times higher, such as 6 times, more preferably at least 8 times higher such as at least 10 times.

33. The composition of claim 1, capable of binding to a receptor selected from the group consisting of cubilin, Scavenger receptor class B, type 1 (SR-B1), ATP-binding cassette 1 (ABC1), Lecithin:cholesterol acyltransferase (LCAT), Cholesteryl-ester transfer protein (CETP), Phospolipid transfer protein (PLTP).

34. The composition of claim 1, wherein the nucleic acid sequence comprises a DNA, a RNA, a PNA, or a LNA sequence.

35. The composition according to claim 1, having an amino acid sequence of sharing at least 70 % sequence identity to one of the sequences SEQ ID NO 2 to SEQ ID NO 11, or SEQ ID NO 14.

36. The composition according to claim 1, having an amino acid sequence sharing at least 70% sequence identify to one of the sequences SEQ ID NO 3 to SEQ ID NO 11, or SEQ ID NO 14.

37. The composition of claim 1, further comprising pharmaceutical acceptable excipients, adjuvants, additives, such as phospholipids, cholesterol, or triglycerides.

38. An apolipoprotein construct having the general formula

- apo-A-X,

- where apo-A is an apolipoprotein component selected from the group consisting of apolipoprotein AI, apolipoprotein AII, apolipoprotein AIV, an functional analogue or variant thereof,

- and X is a heterologous moiety selected from the group consisting of an oligomerising module, and a terminally linked apolipoprotein.

39. The construct of claim 38, further comprising a spacer peptide between the apo-A component and X, wherein the spacer peptide comprises at least two amino acids, such as at least three amino acids, for example at least five amino acids, such as at least ten amino acids, for example at least 15 amino acids, such as at least 20 amino acids, for example at least 30 amino acids, such as at least 40 amino acids, for example at least 50 amino acids, such as at least 60 amino acids, for example at least 70 amino acids, such as at least 80 amino acids, such as at least 90 amino acids such as approximately 100 amino acids.

40. The construct according to claim 39, wherein the spacer is essentially non-immunogenic, and/or is not prone to proteolytic cleavage and/or does not comprise any cystein residues.

41. The construct according to claim 39, wherein the three-dimensional structure of the spacer is linear or substantially linear.

42. The construct according to claim 39, wherein the spacer peptide comprises the amino acid sequence GTKVHMK from tetranectin, amino acid sequence PGTSGQQPSVGQQ and GTSGQ from the connecting strand 3 from human fibronectin, PKPSTPPGSS from the upper hinge region of murine IgG_3, SGGTSGSTSGTGST, AGSSTGSSTGPGSTT or GGSGGAP.

43. The construct according to claim 38, wherein component X comprises at least one amphipatic helix containing apolipoprotein.

44. The construct according to claim 38, wherein the apolipoprotein comprises at least one apolipoprotein A-I, apolipoprotein A-II, apolipoprotein A-IV, Apolipoprotein E, an analogue or variant thereof.

45. The construct of claim 44, wherein the analogue or variant is capable of eliciting substantially the same physiological response as the apolipoprotein-A-I, A-II or A-IV.

46. The construct of claim 38, wherein the oligomerising module is a dimerising module.

47. The construct of claim 38, wherein the oligomerising module is a trimerising module.

48. The construct of claim 38, wherein the oligomerising module is a tetramerising modul.

49. The construct of claim 38, wherein the oligomerising module is a multimerising module.

50. The construct of claim 38, wherein the oligomerising module is of non-peptide nature, such as a nucleic acid sequence comprising a DNA, a RNA, a PNA, or a LNA sequence..

51. The construct of claim 47, wherein the trimerising module is from tetranectin.

52. The construct of claim 51, wherein the tetranectin trimerising module is capable of forming a stable complex with other tetranectin trimerising modules.

53. The construct of the claims 52, wherein the stable complex includes a coiled coil structure.

54. The construct of claim 53, wherein the coiled coil structure is a triple alpha helical coiled coil.

55. The construct of the claims 51, wherein the trimerising module comprising two tetranectin trimerising modules linked by a spacer moiety, which allows both of the two tetranectin trimerising modules to take part in a complex formation with a third tetranectin trimerising module not being part of the apolipoprotein construct.

56. The construct of the claims 51, wherein at least one tetranectin trimerising module is selected from the group consisting of human tetranectin, murine tetranectin or C-type lectin of human, bovine or shark cartilage.

57. The construct of the claims 51, wherein the tetranectin trimerising module comprises a sequence having at least 68 % sequence identity with the sequence of SEQ ID NO 12.

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58. The construct of claim 57, wherein the cystein residue no. 50 is substituted by a serine residue, a threonine residue, or a methionine residue.

59. The construct of claim 47, wherein the trimerisation module has at least 68 % sequence identity with the Trip A module (SEQ ID NO 13).

60. The construct of claim 47, comprising the trimerisation module from the collectin neck region.

61. The construct of claim 38, further comprising at least one carbohydrate moiety.

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62. The construct according to claim 38, having an amino acid sequence sharing at least 70% sequence identity to one of the sequences SEQ ID NO 3 to SEQ ID NO 11, or SEQ ID NO 14.

63. Nucleic acid comprising a sequence of nucleotides encoding an apolipoprotein construct as defined in claim 1.

64. Nucleic acid according to claim 63, encoding an amino acid sequence sharing at least 70 % sequence identity to any of SEQ ID NO 2 to SEQ ID NO 11 or SEQ ID NO 14, preferably to any of SEQ ID NO 3 to SEQ ID NO 11, or SEQ ID NO 14.

65. The nucleic acid of claim 63, wherein the encoding sequence is operably linked to a regulatory sequence for expression of the protein construct.

66. A vector comprising the nucleic acid of claim 63.

67. A transformed host cell, comprising a nucleic acid sequence as defined in claim 63.

68. A method for the production of an apolipoprotein construct as defined in the claims 1, comprising the steps of:

- culturing a transformed host cell under conditions promoting the expression of a protein construct according to claims 1,
- obtaining and recovering said protein construct,
- optionally, further processing said protein construct.

69. A method for treating a patient having a condition related to cholesterol, phospholipids and triacylglycerides LDL and HDL disorders, and arteriosclerotic diseases comprising administering to the individual a pharmaceutical composition according to the claims 1.

70. The method of claim 69, wherein the pharmaceutical composition is administered intravenously, intraarterially, intramusculary, transdermally, pulmonary, subcutaneously, intradermally, intratechally, through the buccal-,

anal-, vaginal-, conjunctival-, or intranasal tissue, or by inoculation into tissue, such as tumour tissue, or by an implant, or orally.

71. The method of claim 69, comprising administering to an individual a composition comprising at least 50 mg apolipoprotein construct per week, preferably at least at least 100 mg/week, for example at least 250 mg/week, such as at least 500 mg/week, for example at least 750 mg/week such as at least 1000 mg/week, for example at least 1250 mg/week, such as at least 1500 mg/week, for example at least 2000 mg/week, such as at least 2500 mg/week, for example at least 5000 mg/week.

72. The method of claim 69, comprising administration during 1, 2, 3, 4, 5, 6, 7, 8 or up to 10 days.

73. The method of claim 69, comprising administering at least 10 mg/kg body weight, such as at least 20 mg/kg body weight, for example at least 30 mg/kg, such as at least 40 mg/kg, for example at least 50 mg/kg, such as at least 60 mg/kg, for example at least 70 mg/kg, such as at least 75 mg/kg, for example at least 90 mg/kg, such as at least 100 mg/kg, for example at least 125 mg/kg, such as at least 150 mg/kg, for example at least 200 mg/kg, such as at least 250 mg/kg, for example at least 300 mg/kg, such as at least 400 mg/kg, for example at least 500 mg/kg, such as at least 600 mg/kg, for example at least 700 mg/kg, such as at least 800 mg/kg, for example at least 900 mg/kg, such as at least 1000 mg/kg.

74. The method of claim 69, comprising administering a dose of a pharmaceutical composition once a week.

75. The method of claim 69, comprising administering a dose of a pharmaceutical composition once every second week, or once every third week, or once every fourth week.

76. The method of claim 69, for the treatment and/or prevention of arterosclerosis.

77. The method of claim 69, for removal of endotoxins.

78. The method of claim 69, in the treatment of angina pectoris.

79. The method of claim 69, in the treatment of myocardial infarction.

80. The method of claim 69, in the treatment of plaque angina pectoris or unstable angina pectoris.

81. The method of claim 69, in the treatment of arterial stenoses such as claudicatio, carotis stenosis or cerebral arterial stenosis.

82. A method for treating a patient having a condition related to cholesterol, phospholipids and triacylglycerides, LDL and HDL disorders, and arteriosclerotic diseases comprising transfecting at least one cell population with a nucleic acid sequence as defined in the claims 63.

83. The method of claim 82, wherein the at least one cell population comprises macrophages.

84. The method of claim 82, wherein the at least one cell population comprises liver cells.